PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 47/12, 31/445, A61P 1/00 — A1

(11) International Publication Number: **WO 00/66170**

(43) International Publication Date: 9 November 2000 (09.11.00)

(21) International Application Number: PCT/EP00/03739

(22) International Filing Date: 20 April 2000 (20.04.00)

(30) Priority Data:
99201335.9 29 April 1999 (29.04.99) EP

(71) Applicant *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; Patent Department, Turnhoutseweg 30, B–2340 Beerse (BE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DE PROOST, Eddy, André, Josée [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B–2340 Beerse (BE).

(74) Agent: VERBERCKMOES, Filip; Janssen Pharmaceutica N.V., Patent Department, Turnhoutseweg 30, B–2340 Beerse (BE).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PRUCALOPRIDE ORAL SOLUTION

(57) Abstract

The present invention is concerned with an oral aqueous solution comprising prucalopride or pharmaceutically acceptable acid addition salts thereof having good organoleptic properties.

FOR THE PURPOSES OF INFORMATION ONLY

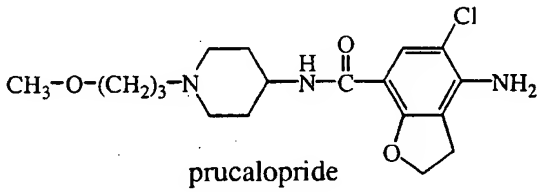
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PRUCALOPRIDE ORAL SOLUTION

The present invention concerns an oral aqueous solution comprising prucalopride or pharmaceutically acceptable acid addition salts thereof having good organoleptic properties.

Prucalopride, which is the generic name for the (1:1) succinic acid addition salt of 4-amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofuran-carboxamide, has enterokinetic properties, *i.e.* it has strong gastrointestinal prokinetic activity.



prucalopride

Prucalopride facilitates both cholinergic and non-cholinergic non-adrenergic (NANC) excitatory neurotransmission and stimulates colonic motility and defecation in animals. It has no affinity for 5-HT_{2A} and 5-HT_3 receptors but is a potent and selective agonist of 5-HT_4 receptors. Prucalopride induces giant contractions in the colon that are propagated over the length of the colon as a peristaltic wave and therefore has significant motility enhancing effects on the large intestine.

Formulations comprising prucalopride are believed of potential use in the treatment of conditions associated with a poorly functioning bladder such as, e.g. urinary incontinence or urinary retention.

Prucalopride is generically described in EP-0,445,862-A1, published on 11 September 1991, and is specifically disclosed in WO-96/16060, published on 30 May 1996.

Administration of an oral dosage form is the preferred route of administration for many pharmaceuticals because it provides for easy, low-cost administration. However some patients such as children or elderly people can have problems when requested to swallow a solid formulation such as a tablet or a capsule. Hence the development of a liquid oral formulation is therefore desirable since it offers improved patient compliance.

EP-0,445,862-A1 discloses an oral solution which comprises prucalopride only in a generic way.

When an aqueous oral solution comprising prucalopride was prepared in accordance with example 22, p. 36, of EP-0,445,862-A2 and administered to a test group of 24 human volunteers in a blind study, it was found that such an oral solution had undesirable organoleptic properties, in particular most volunteers experienced an anaesthetizing feeling on the tongue.

Unexpectedly, it has been found that the prucalopride oral solutions according to the present invention containing benzoic acid do not give an anaesthetizing feeling on the tongue, and thus have acceptable organoleptic properties. Furthermore, the general perception of sweetness and taste were improved.

The term prucalopride as used herein comprises the free base form and the pharmaceutically acceptable acid addition salts thereof. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids. The term addition salt as used hereinabove also comprises the solvates which prucalopride as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

Preferred pharmaceutically acceptable acid addition salts of 4-amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofuran-carboxamide are the hydrochloric acid (1:1) addition salt and the succinic acid (1:1) addition salt.

The solutions according to the present invention have a pH from 2 to 5, preferably from 3.5 to 4.5, most preferably about 4. The pH of the compositions is maintained by a buffer system. Buffer systems comprise mixtures of appropriate amounts of an acid such as phosphoric, succinic, tartaric, lactic, or citric acid, and a base, in particular sodium hydroxide or disodium hydrogen phosphate. Ideally, the buffer has sufficient capacity to remain in the intended pH range upon dilution with a neutral, a slightly acidic or a slightly basic beverage.

Preservatives are included in preparations to kill or inhibit the growth of micro-organisms inadvertently introduced during manufacture or use and are therefore essential ingredients. The choice of a suitable preservative for a preparation depends on pH, compatibility with other ingredients, the route of administration, dose and frequency of administration of the preparation, partition coefficients with ingredients and containers or closures, degree and type of contamination, concentration required, and rate of antimicrobial effect.

In addition to its advantageous organoleptic properties, benzoic acid is also a preservative and is used to prevent microbial spoilage of the oral prucalopride solutions in a concentration from 0.5 mg/ml to 3 mg/ml, preferably from 1 mg/ml to 2 mg/ml, most preferably 1.5 mg/ml.

The pharmaceutically acceptable sweeteners comprise preferably at least one intense sweetener such as saccharin, sodium or calcium saccharin, aspartame, acesulfame potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, monellin, stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxy*galacto*sucrose), preferably saccharin, sodium or calcium saccharin, and optionally a bulk sweetener such as sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel or honey.

The intense sweetener is conveniently employed in low concentrations. For example, in the case of sodium saccharin, the concentration may range from 0.01% to 0.1% (w/v) based on the total volume of the final formulation, and preferably is about 0.05% (w/v).

The bulk sweetener, such as sorbitol, can effectively be used in larger quantities ranging from about 10% to about 35% (w/v), preferably from about 15% to 30% (w/v), more preferably about 30 % (w/v).

When sorbitol is used as a bulk sweetener it is preferably used as an aqueous solution containing 70% (w/v) of sorbitol.

The pharmaceutically acceptable flavours which can mask the bitter tasting ingredients in the low-dosage formulations are preferably fruit flavours such as cherry, raspberry, black currant, strawberry flavour, caramel chocolate flavour, mint cool flavour, fantasy flavour and the like pharmaceutically acceptable strong flavours. Each flavour may be present in the final composition in a concentration ranging from 0.05% to 1% (w/v).

Combinations of said strong flavours are advantageously used. Preferably a flavour is used that does not undergo any change or loss of taste and colour under the acidic conditions of the formulation.

The subject solutions may be presented in art-known containers such as bottles, spray devices, sachets, and the like. Optionally, the solutions are manufactured in unit-dose containers, e.g. unit-dose sachets or unit-dose bottles.

Further, the present invention relates to the preparation of the described solutions. The preparation involves the intimate mixing of the active ingredient with the carrier ingredients.

In general it is contemplated that a therapeutically effective amount of prucalopride would be from about 0.001 mg/kg to about 1 mg/kg body weight, preferably from about 0.01 mg/kg to about 0.5 mg/kg body weight. A method of treatment may also include administering prucalopride on a regimen of between two or four intakes per day.

The amount of prucalopride, or a pharmaceutically acceptable acid addition salt thereof, required as daily dose in treatment will vary not only with the route of administration, the nature of the condition being treated and the age, weight and condition of the patient and will ultimately be at the discretion of the attendant physician. In general, however, a suitable daily dose will be in the range of from about 0.05 to about 50 mg per day, in particular from about 0.1 to 20 mg per day, more particular from about 0.5 to 10 mg per day, preferably from 2 to 4 mg per day. A suitable daily dose for use in prophylaxis will generally be in the same range. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Administration can be before or after the intake of food (*i.e.* preprandial or postprandial).

Experimental section.

Example 1 : Comparative study

The perception of taste and aftertaste of 2 flavours (cherry flavour 2 and strawberry flavour) in combination with 2 sweeteners (sorbitol 70% (w/v) and sodium saccharin dihydrate) was rated. Therefore oral liquid formulations containing one of the two flavours were evaluated for sweetness, fruit taste, anaesthetizing feeling on the tonge and general perception by 24 volunteers in a blind study.

Table 1 : composition of test formulations

	Formulation (1)	Formulation (2)
Compound	Concentration	Concentration
cherry flavour 2	X1	-
strawberry flavour	-	Y2
sorbitol (70% w/v)	X2	Y2
sodium saccharin dihydrate	X3	Y3
methyl parahydroxybenzoate	1.8 mg	1.8 mg
propyl parahydroxybenzoate	0.2 mg	0.2 mg

In both formulations (1) and (2), sodium hydroxide was added to adjust to pH to 4, and purified water was added to a total volume of 1 ml.

Two three-factor, two level full-factorial screening designs were applied to evaluate the effects of sweetness, fruit taste, anaesthetizing feeling and perception.

Table 1a : independent variables and experimental factors of first series of formulations

Factor	Concentration	Concentration
X1	1 mg/ml	3 mg/ml
X2	150 mg/ml	300 mg/ml
X3	0.5 mg/ml	1 mg/ml

X1 : concentration of cherry flavour 2
X2 : concentration of sorbitol 70% (w/v)
X3 : concentration of sodium saccharin dihydrate

Table 1b : independent variables and experimental factors of second series of formulations

Factor	Concentration	Concentration
Y1	1 mg/ml	3 mg/ml
Y2	150 mg/ml	300 mg/ml
Y3	0.5 mg/ml	1 mg/ml

Y1 : concentration of strawberry
Y2 : concentration of sorbitol 70% (w/v)
Y3 : concentration of sodium saccharin dihydrate

Hence, two formulations (1) and two formulations (2) were submitted to the test panel of 24 volunteers.

The dependent (response) variables (sweetness, fruit taste, e feeling and general score) were scored on a scale of 1 to 10.

Overall, sodium saccharin dihydrate scored better in a concentration of 0.5 mg/ml, sorbitol 70% (w/v) in a concentration of 300 mg/ml.

Strawberry scored better than cherry flavour 2. Strawbery affected the sweetness less than cherry flavour 2 and the fruit taste was more pronounced.

However, an anaesthetizing feeling on the tongue was perceived with all formulations.

Because of the anaesthetizing feeling on the tongue, probably due to the use of parahydroxybenzoates (parabens) as preservative, another experiment was set up with benzoic acid as preservative.

Example 2 : Comparative study

Oral liquid formulations containing one of the two preservatives (parahydroxybenzoates or benzoic acid) were evaluated for sweetness, fruit taste and anaesthetizing feeling on the tongue and general perception by 6 volunteers in a blind study.

Table 2 : composition of test formulations :

	Formulation (3)	Formulation (4)
Compound	Concentration	Concentration
strawberry flavour	3 mg	3 mg
sorbitol (70% w/v)	Z1	Z1
sodium saccharin dihydrate	0.5 mg	0.5 mg
methyl parahydroxybenzoate	1.8 mg	-
propyl parahydroxybenzoate	0.2 mg	-
benzoic acid	-	2 mg

Z1 : concentration of sorbitol 70% (w/v) is 150 mg/ml or 300 mg/ml

In both formulations (3) and (4), sodium hydroxide was added to adjust the pH to 4, and purified water was added to a total volume of 1 ml.

A user specified design was applied to evaluate the effects of sweetness, fruit taste and anaesthetizing feeling and general perception.

The dependent (respons) variables (sweetness, fruit taste, anaesthetizing feeling and general perception) were scored on a scale of 1 to 10. The data were analyzed using one-way ANOVA to determine significant differences between the individual means.

Overall, the anaesthetizing feeling was not observed in the presence of benzoic acid, whereas it was always observed in the oral solutions containing parabens (*i.e.* methyl parahydroxybenzoate and propyl parahydroxybenzoate).

Table 3 lists the composition most widely accepted and recommended by the panel of volunteers.

Table 3 : preferred composition

	Formulation (3)	
Compound	Concentration	
strawberry flavour	3 mg	0.3 % (w/v)
sorbitol (70% w/v)	300 mg	30 % (w/v)
sodium saccharin dihydrate	0.5 mg	0.05 % (w/v)
benzoic acid	2 mg	0.2 % (w/v)

Sodium hydroxide was added to adjust the pH to 4, and purified water was added to a total volume of 1 ml.

Example 3: Oral solution (0.2 mg/ml prucalopride)

The following solution comprises 0.2 mg/ml of prucalopride in its free base form as active ingredient, or 0.264 mg/ml of prucalopride as its succinic acid (1:1) addition salt.

prucalopride succinic acid (1:1) addition salt	264 mg
benzoic acid	1500 mg
sorbitol (70% w/v)	230 ml
sodium saccharin	500 mg
strawberry flavour	3000 mg

+ sodium hydroxide to adjust the pH to a value of 4
+ purified water until a total volume of 1000 ml.

Claims

1. An oral aqueous solution having a pH ranging from 2 to 5 and comprising as active ingredient prucalopride, or a pharmaceutically acceptable acid addition salt thereof, and further containing benzoic acid.

2. An oral solution according to claim 1 wherein the amount of benzoic acid ranges from 0.5 mg/ml to 3 mg/ml.

3. An oral solution according to any of claims 1 to 2 wherein the pharmaceutically acceptable addition salt of prucalopride is the (1:1) succinic acid addition salt.

4. An oral solution according to any of claims 1 to 2 wherein the pharmaceutically acceptable addition salt of prucalopride is the (1:1) hydrochlorid acid addition salt.

5. An oral solution according to any of the preceding claims wherein the pH ranges of from 3.5 to 4.5.

6. An oral solution according to any of the preceding claims further comprising a bulk sweetener in a concentration range from 10% to 35% (w/v) and an intense sweetener in a concentration range from 0.01% to 0.05% (w/v).

7. An oral solution according to claim 6 wherein the bulk sweetener is sorbitol and the intense sweetener is sodium saccharin.

8. An oral solution according to claim 1 comprising the following ingredients :

prucalopride succinic acid (1:1) addition salt	264 mg
benzoic acid	1500 mg
sorbitol (70% w/v)	230 ml
sodium saccharin	500 mg
strawberry flavour	3000 mg

+ sodium hydroxide to adjust the pH to a value of 4
+ purified water until a total volume of 1000 ml.

9. A method of preparing an organoleptically acceptable and oral aqueous solution and comprising as active ingredient prucalopride or a pharmaceutically acceptable acid addition salt thereof, which comprises including benzoic acid in such solution, and adjusting the pH to range from about 2 to 5.

INTERNATIONAL SEARCH REPORT

Inter[redacted]cation No
PCT/EP[redacted]03739

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/12 A61K31/445 A61P1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 16060 A (JANSSEN PHARMACEUTICA NV ;HENDRICKX MARIE LOUISE & HF (BE); DAELE) 30 May 1996 (1996-05-30) cited in the application abstract page 4, line 5 - line 16 claims 1,2 ---	1-9
A	EP 0 445 862 A (JANSSEN PHARMACEUTICA NV) 11 September 1991 (1991-09-11) cited in the application abstract example 22 ---	1-9
A	EP 0 389 037 A (JANSSEN PHARMACEUTICA NV) 26 September 1990 (1990-09-26) abstract example 28 ---	1-9

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 July 2000	12/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Taylor, G.M.

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter[redacted]onal [redacted]ation No
PCT/EP [redacted]03739

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 30640 A (JANSSEN PHARMACEUTICA NV ;SCHUURKES JOANNES ADRIANUS JAC (BE)) 2 June 2000 (2000-06-02) abstract page 3, line 16 - line 23 claims 1-10	1-9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal cation No
PCT/EP 03739

Information patent family members

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9616060 A	30-05-1996	AP	777 A	28-10-1999
		AU	704043 B	15-04-1999
		AU	4299296 A	17-06-1996
		BG	101605 A	27-02-1998
		BR	9509819 A	30-09-1997
		CA	2205573 A	30-05-1996
		CZ	9701555 A	17-09-1997
		EP	0807110 A	19-11-1997
		FI	972203 A	23-05-1997
		HR	950571 A	31-08-1997
		HU	77375 A	28-04-1998
		IL	116101 A	17-08-1999
		JP	9512832 T	22-12-1997
		NO	972143 A	09-05-1997
		NZ	297753 A	27-05-1998
		PL	320297 A	15-09-1997
		SK	65297 A	08-10-1997
		TR	960495 A	21-07-1996
		US	5948794 A	07-09-1999
		US	5854260 A	29-12-1998
EP 0445862 A	11-09-1991	AT	191912 T	15-05-2000
		AU	636012 B	08-04-1993
		AU	7207991 A	12-09-1991
		BG	60381 B	31-01-1995
		CA	2037575 A	07-09-1991
		CN	1054598 A,B	18-09-1991
		CN	1054778 A	25-09-1991
		CS	9100460 A	15-10-1991
		DE	69132119 D	25-05-2000
		FI	911096 A	07-09-1991
		HR	930483 A	31-12-1995
		HU	60733 A	28-10-1992
		HU	9500241 A	28-08-1995
		IL	97018 A	27-11-1995
		JP	2601566 B	16-04-1997
		JP	4211685 A	03-08-1992
		KR	177521 B	20-03-1999
		LT	846 A,B	27-02-1995
		LV	10085 A,B	10-05-1994
		NO	177424 B	06-06-1995
		NZ	237189 A	25-11-1992
		PL	168811 B	30-04-1996
		PL	168384 B	29-02-1996
		PL	168686 B	29-03-1996
		PL	168693 B	29-03-1996
		PL	168356 B	29-02-1996
		PL	169238 B	28-06-1996
		PT	96937 A,B	31-10-1991
		SG	47482 A	17-04-1998
		SI	9110396 A	31-12-1997
		RU	2070884 C	27-12-1996
		US	5185335 A	09-02-1993
		US	5262418 A	16-11-1993
		ZA	9101611 A	25-11-1992
		ZW	2391 A	07-09-1992
EP 0389037 A	26-09-1990	AT	128132 T	15-10-1995

INTERNATIONAL SEARCH REPORT

Information patent family members

Inter[illegible]ication No
PCT/EP[illegible]03739

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0389037 A		AU 616838 B	07-11-1991
		AU 5209190 A	27-09-1990
		CA 2012432 A	22-09-1990
		CN 1045781 A,B	03-10-1990
		CY 1921 A	07-03-1997
		DE 69022453 D	26-10-1995
		DK 389037 T	16-10-1995
		ES 2081340 T	01-03-1996
		FI 101624 B	31-07-1998
		FI 944076 A	05-09-1994
		GR 3017992 T	29-02-1996
		HK 131596 A	26-07-1996
		HU 58322 A	28-02-1992
		HU 9500311 A	28-09-1995
		IE 67184 B	06-03-1996
		IL 93817 A	30-03-1995
		IL 110397 A	26-05-1995
		JP 2289566 A	29-11-1990
		JP 2845341 B	13-01-1999
		KR 163587 B	01-12-1998
		NO 176101 B	24-10-1994
		NZ 232964 A	26-07-1991
		PT 93531 A,B	07-11-1990
		RU 2037492 C	19-06-1995
		US 5552553 A	03-09-1996
		US 5616738 A	01-04-1997
		US 5521314 A	28-05-1996
		US 5576448 A	19-11-1996
		US 5554772 A	10-09-1996
		US 5565582 A	15-10-1996
		US 5616583 A	01-04-1997
		US 5536733 A	16-07-1996
		US 5602129 A	11-02-1997
		US 5610157 A	11-03-1997
		US 5739134 A	14-04-1998
		US 5374637 A	20-12-1994
		ZA 9002188 A	27-11-1991
		ZM 1290 A	31-07-1992
		ZW 3390 A	23-10-1991
WO 0030640 A	02-06-2000	NONE	